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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
STRZELECKA, TERESA E

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 09/26/2002 22

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/503,758	THILLY, WILLIAM G.	
	Examiner	Art Unit	
	Teresa E Strzelecka	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-60* is/are pending in the application.

4a) Of the above claim(s) *1-22, 24, 29-32, 34-58* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23, 25-28, 33, 59, 60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. This Office action is in response to an amendment filed on July 23, 2002.

Response to Arguments

2. Applicant's arguments filed on July 23, 2002 have been fully considered but they are not persuasive. Applicants argue that:

a) amendment to claims 25 and 33, indicating that point mutations can be detected down to a frequency of at least 5×10^{-5} obviates the 35 U.S.C. 102(b) rejection of these claims over Kervinen et al.,

b) the 35 U.S.C. 103(a) rejection of claim 60 over Kervinen et al. and Khrapko et al. is improper, since neither of the references provides express or implied motivation to combine the teachings of these references.

Regarding the first argument, the phrase added to claims 25 and 33 in step a) of the method, which reads "...wherein the set of all inherited point mutations occurring at a frequency at about or above 5×10^{-5} can be identified...", does not obviate the rejection of these claims over Kervinen et al. The fact that the mutation frequencies can be measured down to a certain frequency does not mean that they were actually measured at this level of sensitivity, since this is not an active method step. Therefore the active methods steps are unchanged and claims 25 and 33 are still rejectable over Kervinen et al.

Regarding the second argument, the motivation provided by Khrapko et al. is perfectly applicable to the study of allele frequencies of Kervinen et al., since one of the populations used in that study were nonagenarians (only 89 individuals). If one wanted to detect a harmful allele, expected to decrease in frequency in aged populations, one would want to use the most sensitive

method of mutation detection available, namely, one of Khrapko et al. The rejection of claim 60 is maintained.

3. This Office action is made non-final because of the 35 U.S.C § 112, second paragraph, rejections and art rejection of claim 59.

Claim Rejections - 35 USC § 112

4. Claims 23, 25-28, 33, 59 and 60 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claim 23 recites the limitation "the inherited point mutations" in lines 2 and 7. There is insufficient antecedent basis for this limitation in the claim.

B) Claim 23 recites the limitation "the genes" in lines 2 and 7. There is insufficient antecedent basis for this limitation in the claim.

C) Claim 23 recites the limitation "the frequencies" in lines 4 and 9. There is insufficient antecedent basis for this limitation in the claim.

D) Claim 23 recites the limitation "the sum of the frequency" in line 5 and "the sum of the frequencies" in line 10. There is insufficient antecedent basis for this limitation in the claim.

E) Claim 23 is indefinite because of the limitation "sum of the frequency" in line 5. It is unclear how there can be a sum of one frequency.

F) Claim 25 recites the limitation "the inherited point mutations" in line 2. There is insufficient antecedent basis for this limitation in the claim.

G) Claim 25 recites the limitation "the genes" in lines 2 and 6. There is insufficient antecedent basis for this limitation in the claim.

H) Claim 25 recites the limitation "the set of all inherited point mutations" in lines 3 and 4. There is insufficient antecedent basis for this limitation in the claim.

I) Claim 25 recites the limitation "the set of inherited point mutations" in lines 3 and 4. There is insufficient antecedent basis for this limitation in the claim.

J) Claim 23 recites the limitation "the sum of the frequency" in line 5 and "the sum of the frequencies" in line 10. There is insufficient antecedent basis for this limitation in the claim.

K) Claim 26 recites the limitation "the age-specific decline" in line 5. There is insufficient antecedent basis for this limitation in the claim.

L) Claim 26 is indefinite because of the limitation "... decline of said two or more point mutations...". It is unclear what is meant by a "decline in mutation".

M) Claim 26 is indefinite because of the limitation "... determining if the functions are significantly different...". It is unclear what is considered a "significant" difference in the functions and what properties of the functions are considered (values?).

N) Claim 26 is indefinite because of the limitation "... decline of harmful alleles...". It is unclear what is meant by a "decline in an allele".

O) Claim 33 recites the limitation "the inherited point mutations" in line 3. There is insufficient antecedent basis for this limitation in the claim.

P) Claim 33 recites the limitation "the set of inherited point mutations" in line 7. There is insufficient antecedent basis for this limitation in the claim.

R) Claim 33 recites the limitation "the genes" in lines 3 and 7. There is insufficient antecedent basis for this limitation in the claim.

S) Claim 33 recites the limitation "the frequencies" in line 6 and "the frequency" in line 9. There is insufficient antecedent basis for this limitation in the claim.

T) Claim 59 recites the limitation "the inherited point mutations" in line 1. There is insufficient antecedent basis for this limitation in the claim.

U) Claim 59 recites the limitation "the set of all inherited point mutations" in line 6. There is insufficient antecedent basis for this limitation in the claim.

V) Claim 59 is indefinite because the claims do not recite a final process step which clearly relates back to the preamble. The preamble states that the method is for "a method of identifying the inherited point mutations", but the final process step is "determining which inherited point mutations are deleterious, harmful or beneficial". Therefore, it is unclear as to whether the claim is intended to be limited to a method of identifying point mutations or a method of classifying them as deleterious, harmful or beneficial.

X) Claim 59 is indefinite as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The claim does not recite any active steps.

Y) Claim 60 recites the limitation "the mutant fraction" in line 9. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 25, 33 and 59 are rejected under 35 U.S.C. 102(b) as being anticipated by Kervinen et al. (Atherosclerosis, vol. 105, pp. 89-95, 1994).

Kervinen et al. teach identification of a harmful allele of apolipoprotein E (apo E) and apolipoprotein B (apo B) by determining the frequency of apo E and apo B polymorphisms in populations of young adults, middle-aged adults and nonagenarians. The frequencies of apo E ε4 allele and of apoB EcoRI R- allele were found to be significantly lower in nonagenarians than in young or middle –aged adults, indicating that the presence of these alleles suggests increased risk for coronary heart disease (Abstract; Fig. 2; Table 4; page 93, 94).

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claim 60 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kervinen et al. as applied to claim 25 above, and further in view of Khrapko et al. (1) (Nucl. Acids Res. Vol. 25, pp. 685-693, 1997) and Khrapko et al. (2) (Nucl. Acids Res. Vol. 22, pp. 364-369, 1994).

A) Claim 60 is drawn to identifying point mutations by amplifying a region of a target gene from a pool of DNA fragments isolated from a population, melting and reanneling the PCR products to form a mixture of homo- and heteroduplexes containing point mutations, separating homo- from heteroduplexes and recovering heteroduplexes, amplifying the heteroduplex fragments to produce homoduplex wild-type DNA and homoduplex DNA containing the point mutations, resolving and recovering the DNAs which contain point mutations and sequencing the DNAs to identify the point mutations.

B) Kervinen et al. do not teach using constant denaturant capillary electrophoresis (CDCE) combined with high-fidelity PCR to determine point mutations in DNA samples from populations.

C) Khrapko et al. (1) teach a method of determining point mutations in a DNA sample at a fraction of 10^{-6} or above using constant denaturant capillary electrophoresis (CDCE) combined with high-fidelity PCR. The method comprises the following steps:

a) restriction digest of DNA isolated from cells to obtain a 200 bp DNA fragment with low temperature and high temperature isomelting domains,

b) enrichment of mutant sequences by constant denaturant gel electrophoresis (CDGE),

c) high fidelity PCR amplification resulting in fluorescently labeled products, using *Pfu* polymerase, which has an error rate of $2x10^{-6}$ errors per base per doubling,

d) separation of PCR heteroduplexes from homoduplexes by CDCE and collection of the heteroduplxes,

e) another round of high fidelity PCR in which mutant heteroduplexes are converted into homoduplexes by stopping the PCR reaction when the molar amount of unused primers still exceeds the molar amount of the products,

f) another round of CDCE separation of the homoduplexes,

g) isolation and sequencing of the mutants. (Fig. 1; page 686-689).

Khrapko et al. (2) teach that prior to CDCE separation the DNA fragments are boiled and reannealed, resulting in a mixture of homoduplexes and heteroduplexes, which are then separated based on the differences in their melting temperature in a CDCE capillary column (page 365, paragraphs 6-9; page 366; Fig. 3, 4).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the point mutation detection method of Khrapko et al. (1) and (2) in the method of mutation detection of Kervinen et al.. The motivation to do so, expressly provided by Khrapko et al., would have been that combining CDCE with high fidelity PCR permitted detection of low frequency mutations.

9. No references were found teaching or suggesting claims 23 and 26-28, but they are rejected for other reasons.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E Strzelecka whose telephone number is (703) 306-5877. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached at (703) 308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

TS
September 23, 2002 TS

KENNETH R. HORLICK, PH.D
PRIMARY EXAMINER
9/24/02